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10/070,882	03/11/2002	Richard William Titball	41577/270459	2737

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EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT PAPER NUMBER

1645

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/070,882

Applicant(s)

TITBALL ET AL.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 November 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7-15 and 17-32 ~~is/are~~ are pending in the application. /
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-15 and 17-32 ~~is/are~~ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 11/22/05, 09/26/05 and 06/24/05 in response to the non-final Office Action mailed 03/23/05. The amendment filed 11/22/05 is compliant. With this, Applicants have amended the specification and claims, and have submitted an abstract.

Status of Claims

2) Claims 1, 2, 7, 10-12, 15, 17 and 19-22 have been amended via the amendment filed 11/22/05.

New claims 23-32 have been added via the amendment filed 11/22/05.

Claims 1-4, 7-15 and 17-32 are pending and are under examination.

Objection(s) to Specification

3) (A) The specification is objected to for failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP 608.01(o).

(a) Claim 1, as amended currently, includes the added limitation: placing 'a nucleotide sequence encoding' the protein', which lacks antecedent basis in the specification.

(b) The limitations in the new method claims 23-32 lack antecedent basis in the specification.

(B) The instant specification is confusing and/or incorrect in the limitation: '*Schistoma mansoni*'. For example, see lines 15 and 16 of page 7 of the specification.

Objection(s) Withdrawn

4) The objection to the specification made in paragraph 7(A) of the Office Action mailed 03/23/05 is withdrawn in light of Applicants' amendments to the specification.

5) The objection to the specification made in paragraph 7(B) of the Office Action mailed 03/23/05 is withdrawn in light of Applicants' amendments to the specification.

6) The objection to the specification made in paragraph 7(C) of the Office Action mailed 03/23/05 is withdrawn in light of Applicants' amendments to the specification.

7) The objection to claims 1, 2 and 20 made in paragraph 15 of the Office Action mailed

03/23/05 is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Withdrawn

- 8)** The rejection of claims 1, 2, 11, 15, 22 and those dependent therefrom made in paragraph 8 of the Office Action mailed 03/23/05 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is withdrawn in light of Applicants' amendments to the claims.
- 9)** The rejection of claims 1, 2, 11, 15, 22 and those dependent therefrom made in paragraph 9 of the Office Action mailed 03/23/05 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' amendments to the claims.
- 10)** The rejection of claim 2 made in paragraph 11(a) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.
- 11)** The rejection of claim 1 made in paragraph 11(b) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.
- 12)** The rejection of claims 11 and 22 made in paragraph 11(c) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims.
- 13)** The rejection of claim 1 made in paragraph 11(d) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.
- 14)** The rejection of claim 1 made in paragraph 11(e) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.
- 15)** The rejection of claim 1 made in paragraph 11(f) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.
- 16)** The rejection of claim 2 made in paragraph 11(g) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

amendments to the claim.

17) The rejection of claim 2 made in paragraph 11(h) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

18) The rejection of claims 7 and 19 made in paragraph 11(i) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims.

19) The rejection of claim 10 made in paragraph 11(j) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

20) The rejection of claim 12 made in paragraph 11(k) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

21) The rejection of claim 15 made in paragraph 11(l) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

22) The rejection of claim 17 made in paragraph 11(m) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

23) The rejection of claim 20 made in paragraph 11(n) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

24) The rejection of claim 21 made in paragraph 11(o) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

25) The rejection of claim 22 made in paragraph 11(p) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

26) The rejection of claims 3, 4, 7-15 and 17-22 made in paragraph 11(q) of the Office Action mailed 03/23/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the base claim.

Rejection(s) Maintained

27) The rejection of claims 2-4, 7-15, 17-19, 21 and 22 made in paragraph 13 of the Office Action mailed 03/23/05 under 35 U.S.C § 102(e) as being anticipated by Titball *et al.* (US 5,985,285, filed 09/15/1997) ('285), is maintained for reasons set forth therein and herebelow.

Applicants submit that while Titball *et al.* disclose a range of promoters, the Titball patent fails to disclose P_{phoP} as a promoter in an expression construct. Applicants assert that the only promoter exemplified in the Titball patent is the *lac* promoter. Applicants state that lines 46-48 in column 3 state that the *lac* promoter and the *nirB* promoter are preferred.

Applicants' arguments have been carefully considered, but are not persuasive. Contrary to Applicants' assertion, Titball *et al.* ('285) disclosed the F1 gene expression vector plasmid and its expression in *S. typhimurium* (see columns 2, 12 and 15-18). The DNA encoding the protein is positioned in frame (i.e., operably interconnected with) with the *in-vivo* inducible promoter, PhoP (see claims 44, 18, 16, 15, 14, 33, 32, 5, 3, 2 and 1). Thus, as set forth previously, Titball *et al.* ('285) disclosed a live oral vaccine comprising a pharmaceutically acceptable carrier or an adjuvant and a human or animal gut colonizing microorganism that is transformed with a recombinant DNA construct expressing the heterologous F1 antigen of *Yersinia pestis* under the control of *phoP in vivo* inducible promoter (i.e., the P_{phoP} promoter, a fragment or variant thereof containing no further elements of the *phoP* gene) wherein the DNA is positioned in frame with the promoter. Titball *et al.* ('285) disclosed a method of protecting a human or animal from *Yersinia pestis* infection by administering the live oral vaccine. The vaccine when administered to a human or animal induces local stimulation of the gut-associated lymphoid tissue and stimulates a secretory IgA response by trafficking lymphocytes through the common mucosal immune system (see abstract; claims, particularly claims 44 and 33; Examples; and first full paragraph in column 3). The microorganism is an attenuated *S. typhimurium* or *S. typhi* (see paragraph bridging columns 2 and 3; and first full paragraph in column 3). The rejection stands.

28) The rejection of claims 2-4, 7-15, 17-19, 21 and 22 made in paragraph 14 of the Office

Action mailed 03/23/05 under 35 U.S.C § 102(b) as being anticipated by Titball *et al.* (WO 96/28551 – Applicants' IDS) ('551), is maintained for reasons set forth therein and herebelow.

Applicants agree that the Titball PCT disclosure teaches a range of promoters. However, Applicants argue that the Titball PCT disclosure fails to disclose P_{phoP} as a promoter in an expression construct, or constructs that utilize the P_{phoP} promoter. Applicants submit that there is no teaching to one of skill in the art to select the P_{phoP} promoter for use in constructs of the type disclosed herein. Applicants state that they are the ones who have observed that constructs utilizing the P_{phoP} promoter have an unexpected advantage in terms of the expression in mucosal effector cells.

Applicants' arguments have been carefully considered, but are not persuasive. Contrary to Applicants' assertion, Titball *et al.* ('551) disclosed the F1 gene expression vector plasmid and its expression in *S. typhimurium* (see pages 78, 22 and 23). The gene encoding the protein is positioned in frame (i.e., operably interconnected with) with the *in-vivo* inducible promoter, PhoP (see claims 46, 45, 17, 18, 35, 34, 5, 4, 3, 2 and 1). Thus, as set forth previously, Titball *et al.* ('551) disclosed a live oral vaccine comprising a pharmaceutically acceptable carrier or an adjuvant and a human or animal gut colonizing microorganism that is transformed with a recombinant DNA construct expressing the heterologous F1 antigen of *Yersinia pestis* under the control of PhoP *in vivo* inducible promoter (i.e., the P_{phoP} promoter, a fragment or variant thereof containing no further elements of the *phoP* gene) wherein the DNA is positioned in frame with the promoter. Titball *et al.* ('551) disclosed a method of protecting a human or animal from *Yersinia pestis* infection by administering the live oral vaccine. The vaccine when administered to a human or animal induces local stimulation of the gut-associated lymphoid tissue and stimulates a secretory IgA response by trafficking lymphocytes through the common mucosal immune system (see abstract; claims, particularly claims 46 and 35; Examples; and first full paragraph in column 3). The microorganism is an attenuated *S. typhimurium* or *S. typhi* (see paragraphs 1-3 on page 4). The rejection stands.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

29) Claims 23-32 are rejected under 35 U.S.C § 112, first paragraph, paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 23-32 depend from claim 1, encompass a method of enhancing expression of a desired protein at mucosal sites, and include limitations that are not supported in the instant specification, as originally filed. Applicants have not pointed to specific parts of the specification, as originally filed, where descriptive support can be found for the new claims. The only location wherein the recitation of 'a method of enhancing expression of a desired protein at mucosal effector sites' as claimed in the independent claim 1 can be found appears to at lines 6-11 of page 4 of the instant specification. The specification does not appear to describe the embodiments now claimed in new claims 23-32. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or invited to point to specific pages and line numbers in the originally filed specification where support for recitations can be found.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

30) Claims 1, 2-4, 7-15 and 17-32 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and indefinite in the limitations: 'enhancing expression of a desired protein at mucosal effector sites' and 'causing expression in mucosal cells', because it is unclear how 'causing expression' of a desired protein 'in mucosal cells' can result in a method of 'enhancing expression' of the desired protein 'at mucosal effector sites'. The claim appears to be internally inconsistent in scope. Are 'mucosal effector sites' located within 'mucosal cells'? Do 'mucosal cells' comprise the recited nucleotide sequence under the control of the recited promoter having SEQ ID NO: 2 and express the desired protein? Clarification is requested.

(b) Claim 2 is vague and indefinite in the limitation: 'to which it is administered',

because it is unclear whether 'it' that is administered to a mammal is the claimed 'construct' or the recited 'protein'. Clarification/correction is requested.

(c) Analogous criticism and rejection apply to claim 23.

(d) Claims 11, 22 and 30 are vague in the limitation: 'protein comprises an F1-antigen of *Yersinia pestis*'. Does it mean that there are more than one F1 antigens of *Yersinia pestis* and the recited protein comprises one such 'F1-antigen'? Is this 'protein comprising an F1-antigen', for example a fusion protein that comprises an F1-antigen of *Yersinia pestis*, or a protein that is the F1-antigen of *Yersinia pestis*? Clarification/correction is requested.

(e) New claim 23 is vague, indefinite and confusing in the limitation 'method of claim 1 a nucleic acid which encodes a protein'. Claim 23 depends from claim 1 which recites a nucleotide sequence encoding the desired protein. Is 'a protein' encoded by 'a nucleic acid' that is recited in line 2 of claim 23 an additional encoded protein other than the one encoded by the nucleotide sequence recited in claim 1?

(f) Analogous criticism and rejection apply to the new claim 24, which depends from claim 1, with regard to the limitation: 'a promoter having a nucleotide sequence of SEQ ID NO: 2'.

(g) For the purpose of distinctly claiming the subject matter, in line 3 of claim 1, it is suggested that Applicants replace the limitation 'a nucleotide sequence of SEQ ID NO: 2' with the limitation --the nucleotide sequence of SEQ ID NO: 2--.

(h) Claim 20 is vague and indefinite in the limitation 'the sequence of SEQ ID NO: 2' without particularly reciting that the sequence is --the nucleotide sequence of SEQ ID NO: 2--.

(i) Claim 27 is inconsistent with claim 8 or claim 26 with regard to the limitation: '*Salmonella Spp*'.

(j) Claims 3, 4, 7-15 and 17-32, which depend directly or indirectly from claim 1 or claim 2, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

31) Claims 1-4, 7-15 and 17-22 stand rejected.

32) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions

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24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of after-final amendments is (571) 273-8300.

33) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

34) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

February, 2006


S. DEVI, PH.D.
PRIMARY EXAMINER